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BRAIN AND HEART ACCUMULATION OF BROMOTRIFLUOROMETHANE

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The experiments reported herein were conducted according to the "Guide for Laboratory Animal Facilities and Care," 1965 prepared by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences – National Research Council.

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13. ABSTRACT

One hundred seventy-six albino rats were divided into 11 groups of 16 rats each. The rats were exposed by groups to 70-75% $CBrF_3$ in O_2 for 5 minutes. The rats were serially killed throughout the exposure and 55-minute postexposure period. The brains and hearts from the rats in 10 of the 11 groups were rapidly excised and placed in vials of heptane. The contents of the vials were subsequently analyzed for $CBrF_3$. Blood samples were obtained from the rats in the 11th group which was treated identically to the other 10 groups. After the first minute of the 5-minute exposure, the concentration of $CBrF_3$ in the brains rose approximately twice as rapidly as the concentration in the hearts. At the end of the 5-minute exposure the brain concentration was approximately 50% greater than the heart concentration. The heart concentration did not differ significantly from the blood concentration. The postexposure rates of decline of the tissue concentrations of $CBrF_3$ were approximately equal. The brain required almost exactly 1 minute longer to reach a given concentration than the heart. Only trace amounts of $CBrF_3$ were detectable beyond 10 minutes postexposure.

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SUMMARY

One hundred seventy-six albino rats were divided into 11 groups of 16 rats each. The rats were exposed by groups to 70-75% $CBrF_3$ in O_2 for 5 minutes. The rats were serially killed throughout the exposure and 55-minute postexposure period. The brains and hearts from the rats in 10 of the 11 groups were rapidly excised and placed in vials of heptane. The contents of the vials were subsequently analyzed for $CBrF_3$. Blood samples were obtained from the rats in the 11th group which was treated identically to the other 10 groups. After the first minute of the 5-minute exposure, the concentration of $CBrF_3$ in the brains rose approximately twice as rapidly as the concentration in the hearts. At the end of the 5-minute exposure the brain concentration was approximately 50% greater than the heart concentration. The heart concentration did not differ significantly from the blood concentration. The postexposure rates of decline of the tissue concentrations of $CBrF_3$ were approximately equal. The brain required almost exactly 1 minute longer to reach a given concentration than the heart. Only trace amounts of $CBrF_3$ were detectable beyond 10 minutes postexposure.

FOREWORD

The research reported in this paper was performed in the Toxicology Branch, Toxic Hazards Division, Aerospace Medical Research Laboratory, Aerospace Medical Division, Air Force Systems Command, Wright-Patterson Air Force Base, Ohio 45433. The authors wish to thank Sgt Doyle Manion for his assistance in performing these experiments. This technical report has been reviewed and is approved.

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SECTION I
INTRODUCTION

Bromotrifluoromethane is a gas which boils at -58°C and is stored as a liquid under pressure. The United States Air Force and other governmental agencies are interested in $CBrF_3$ as a potential fire-extinguishing chemical for use both in closed and open environments (Botteri and Manheim, 1969).

The inhalation exposure of monkeys and dogs to 20-80% $CBrF_3$ in O_2 has been shown to cause a wide range of pharmacologic effects (Van Stee & Back, 1969). Unifocal and multifocal ventricular cardiac arrhythmias, decreased myocardial contractility, and decreased peripheral vascular resistance were observed during the first 1-2 minutes of exposure to concentrations of $CBrF_3$ greater than 50% (Van Stee & Back, 1971a, 1971b, Van Stee et al., 1971). Within 3-4 minutes alterations in the electroencephalogram were seen (Van Stee et al., 1970).

The time courses of the $CBrF_3$ effects were different for those effects mediated by the heart and those mediated by the nervous system. This could be explained in part on the basis of a preferential uptake by nervous tissue of $CBrF_3$. The evaluation of this possibility was the purpose of this short study.

SECTION II
METHODS

One hundred seventy-six albino rats (Charles River) weighing 300 to 450 gm were divided into 11 groups of 16 rats each. Both sexes were used indiscriminately. A 50-liter exposure chamber was fabricated from a corrugated paper box in the shape of a truncated pyramid and enclosed in polyethylene. $CBrF_3$ and O_2 were delivered from cylinders under pressure through flowmeters and introduced into the exposure chamber in a ratio of about 3:1. The gas delivery and sampling tubes were located in the chamber approximately 10 cm from the bottom and on opposite sides of the chamber. Intermittent chamber atmospheric samples were withdrawn through the sampling tube and the relative concentrations of $CBrF_3$ and O_2 determined. The chamber was purged prior to exposure with the $CBrF_3$-O_2 mixture until the $CBrF_3$ concentration exceeded 70%. Irrigation of the chamber was continuous and the $CBrF_3$ concentration was determined at 1-minute intervals throughout the exposure period.

Rats were stunned by a blow to the head and then decapitated. One operator quickly removed most of the brain tissue while another operator removed the heart. Tissues were quickly dipped in 0.9% NaCl solution, transferred to glass containers of n-heptane and tightly capped. The tissues were in the capped containers within 30 seconds ~~of~~ AFTER removal of the rats from the exposure chamber.

Groups of 16 rats were selected at random. ~~from the population available for the study.~~ Immediately prior to each exposure ~~the~~ OF rat was

killed and the brain and heart removed to serve as the preexposure control. The 15 remaining rats were then placed in the chamber. Minute 0 of the experiment coincided with the placement of the rats in the exposure chamber. Individual rats were removed at minutes 1, 2, 3, 4, and 5 of the exposure period and the tissues obtained. At minute 5 the remaining rats were removed from the chamber and placed in a ventilated box, ~~in~~ room air. The tissues from the 10 rats were obtained at minutes 6, 7, 8, 9, 10, 15, 20, 30, 45, and 60. This procedure was repeated 10 times. During the 11th experiment intracardiac blood samples were obtained according to an identical sampling schedule. All ~~of the~~ other conditions of the previous 10 experiments were met during the 11th experiment.

The tissue analyses of $CBrF_3$ were performed using a gas chromatographic techniq~~ue employing~~ and an electron capture detector. } Ref. would be appropriate

Comparisons of pair~~s of~~ed mean values were performed, where appropriate, using Student's t-test. A comparison of the mean values of the chamber concentrations of $CBrF_3$ was performed using a one-way analysis of variance (Freund et al., 1960).

SECTION III
RESULTS

Figure 1 illustrates the results of the periodic analyses of the $CBrF_3$ mixture in the exposure chamber during 9 of the 10 exposures. These determinations were not available for one of the runs. The mean concentration rose significantly during the exposure periods and varied from

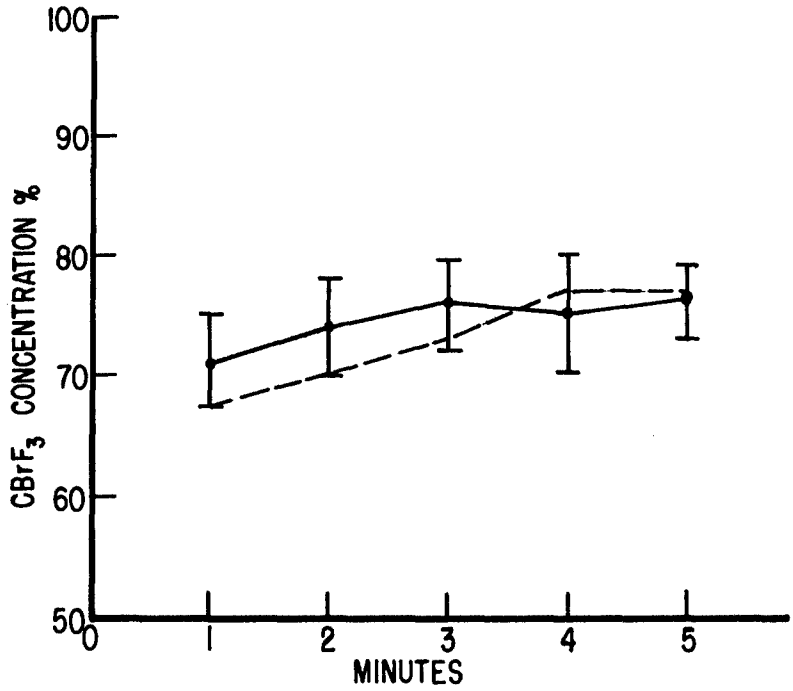

Figure 1: The concentration of $CBrF_3$ in the exposure chamber during 5-minute exposures of rats for the purpose of measuring the uptake of $CBrF_3$ by brain and heart tissue (n=9, mean $\pm$ SD).

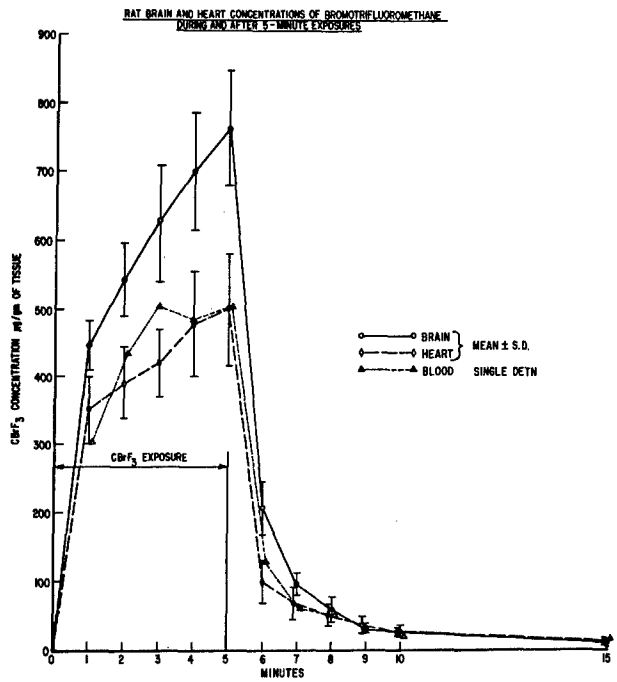

Figure 2: Rat brain and heart concentrations of $CBrF_3$ during and after 5-minute exposures to 71-76% $CBrF_3$ in O_2 (n=10, mean $\pm$ SD). The broken line represents blood concentrations of $CBrF_3$ observed during an experiment in which the conditions were similar to those of the brain-heart experiments (n=1).

71% to 76% $CBrF_3$. The broken line represents the $CBrF_3$ concentrations during the 11th experiment in which the blood concentration of $CBrF_3$ was determined. The concentrations in the 11th experiment were just outside the 95% confidence interval during minutes 1-3 when compared with the chamber concentrations during the brain-heart experiments. There was no statistically significant difference between the concentrations during the 4th and 5th exposure minutes.

Figure 2 illustrates the results of the analyses of the tissue concentrations of $CBrF_3$. The mean brain concentration of $CBrF_3$ reached 445 µg/gm of tissue after the first minute and rose at an average rate of 79 µg/gm/min to 760 µg/gm of tissue. The mean heart concentration reached 350 µg/gm of tissue during the first minute and rose at an average rate of 35 µg/gm/min to 500 µg/gm of tissue. The brain concentrations of $CBrF_3$ were significantly higher than those of the heart at all times during the 5 minute exposure ~~from minute 1 through minute 5~~. The brain concentrations of $CBrF_3$ rose approximately twice as rapidly and to 50% higher levels than the heart during 5-minute exposures to 71-76% $CBrF_3$. The rates of decay of the respective tissue concentrations of $CBrF_3$ were comparable. One minute postexposure the brain concentration was 210 µg/gm of tissue and the heart concentration was 100 µg/gm of tissue, a statistically significant difference (1% level). At 2 minutes postexposure the respective concentrations were 95 and 68 µg/gm, a statistically significant difference (1% level). ~~From~~ After 3 minutes postexposure the differences between ~~the~~ brain and heart concentrations of $CBrF_3$ were not significant. The

blood concentrations closely paralleled the heart concentrations and they differed significantly from the brain concentrations. The tissue concentrations of $CBrF_3$ approached zero asymptotically postexposure. No significant differences in $CBrF_3$ concentration were seen among the three tissues beyond 2 minutes postexposure to the end of the experiment 55 minutes postexposure.

DISCUSSION

Van Stee et al(6)(1971) demonstrated the difference in the recovery times of the peripheral vasomotor tone and myocardial contractility in a dog following a 5-minute exposure to 80% $CBrF_3$. The index of contractility, dp/dt, returned to preexposure levels during the period 0.5 - 0.7 minutes postexposure. The blood flow through the right femoral artery rose from an already elevated level during this period. The blood flow then began to drop rapidly from 0.8-minutes postexposure and had returned to preexposure levels by 4-minutes postexposure. Results of this study proved that the flow change through the femoral artery was mediated by a change in vasomotor tone. Part of the observed change in vasomotor tone was apparently the result of ganglionic blockade, an effect reported for halothane which has some pharmacologic properties similar to those of $CBrF_3$ (Dobkin & Su, 1966; Dundee, 1967). In addition to an element of ganglionic blockade, however, a decrease in central sympathetic outflow may also occur. A conclusion was drawn that the observed myocardial function returned earlier than the observed central nervous system function following a 5-minute exposure to 80% $CBrF_3$.

The heptane-water partition coefficient for $CBrF_3$ ~~has been determined in our laboratory to be~~ approximately 9.8.[15] It is a non-polar substance which readily crosses the blood-brain barrier. Because of its solubility in organic solvents, $CBrF_3$ would be expected to accumulate in the central nervous system because of its relatively high lipid content compared to

that of the heart.

The observation that the brain does, indeed, accumulate a significantly higher concentration of $CBrF_3$ than the heart may provide a partial explanation of the difference in functional recovery times. If one made the dubious assumption for the purpose of the discussion that the functional effects of a given amount of $CBrF_3$ were approximately equivalent for brain and heart tissue it would follow from these data that the postexposure effect would be expected to persist in the brain for about 2 minutes longer than the heart, which is the case (Van Stee et al, 1971).

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